Urea and Thiourea Complexes in Separating Organic Compounds

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One of the newest separation techniques that has already become a useful and powerful tool is the formation of crystalline inclusion complexes of urea or thiourea with organic compounds. The subject is briefly reviewed under the headings: preparation, analysis, and decomposition of complexes, and applications in the petroleum and fat fields. Both fundamental and practical applications of the complexes are described.

ONE of the newest separation techniques and one which has already become a useful and powerful tool is the formation of crystalline inclusion complexes (adducts or molecular compounds as they are frequently called) of urea or thiourea with organic compounds. These inclusion complexes have the unique characteristic of permitting the isolation and handling of gases, liquids, and solids, in a solid form. Since the substance being separated is included in the crystalline framework of another molecular species (urea or thiourea), a weight and volume increase are experienced and the handling, manipulation, and storage of small, and even large, quantities of desired substances are often considerably simplified and improved.

A complex is a substance, usually crystalline, consisting of a combination of two or more compounds each capable of separate existence and having no obvious means of chemical union. An inclusion complex, of which urea and thiourea complexes are examples, is a complex in which one of the components is contained in the framework of the other, the framework consisting of a channel, a cage, or layers. Urea and thiourea complexes are members of the channel type of inclusion complexes, and this paper will be devoted exclusively to them. Time and space limitations prevent a complete discussion of all types of inclusion complexes, but several reviews are now available (*17, 38, 49, 50, 55, 60, 81, 85*).

Urea Complexes

At present, the most important and widely used, as well as the most thoroughly investigated class of inclusion complexes, are the urea complexes. Some of the reasons for the emphasis on urea complexes are that some potentially important industrial uses have been discovered for them; urea is plentiful and cheap; its complexes are easy to make and have interesting fundamental properties.

The discovery of urea complexes is credited to Bengen. In a German patent application filed in 1940 (*8*) and uncovered by a technical Oil Mission (*40*) of the Allies after World War II, he briefly reported that straight chain aliphatic compounds containing six or more carbon atoms formed well-defined, crystalline complexes with urea, whereas branched chain and cyclic compounds did not. This discovery, which was accidental, arose out of research Bengen was conducting on milk (*7*).

Bengen studied the preparation of complexes from straight chain hydrocarbons, acids, esters, alcohols, aldehydes, and ketones. Subsequently it was shown by numerous other workers (*6, 16, 37, 41, 47, 52, 61, 64, 74–76, 79, 80, 86*), notably Schlenk, that these and many other classes of straight chain compounds also formed urea complexes.

In general, ease of formation and stability of urea complexes increase with increasing chain length. The maximum chain length reported to form a urea complex with hydrocarbons is C_{50}; with esters, C_{46}. These should not necessarily be considered upper limits, however (*19*). In no case studied so far is any complex stable above about 133° C., the melting point of urea. All urea complexes apparently have the melting point of urea. Table I shows how the room temperature stability of urea complexes of aliphatic ketones as measured by half-life times increases with chain length (*64*). At a chain length of 7 or fewer carbon atoms the complex will not endure very long. The rate of increase of half-life time with increasing chain length, however, suggests that at a chain length of 8 or more carbon atoms, the stability of the complex will be, and in fact is, high. In urea complexes of other homologous series of *n*-aliphatic compounds, about 8 carbon atoms represent the shortest chain length of included compound which yields a complex stable at room temperature for long periods of time. In general, the stability of urea complexes varies in some inverse way with the vapor pressure of the included compound. Vapor pressure, however, is not the sole criterion for complex stability, although it is an important factor. Table I indicates that urea complexes should not be heated excessively.

Table I. Half-Life Times of Urea-Ketone Complexes

Compound in Complex	B.P., ° C.	Vapor Pressure, Mm., 25° C.	Half-Life Time, Min.
Acetone	56.5	230	4
Methyl ethyl ketone	79.6	100	10
Diethyl ketone	102.7	18	140
Di-*n*-propyl ketone	143.7	1.1	1500

In general, the principles originally proposed by Bengen still apply with some minor exceptions. For example, although he thought that a minimum chain length of 6 carbon atoms was necessary for complex formation, Schlenk (*64*) has obtained urea complexes from some 3-carbon (nonvolatile) compounds. Also, contrary to the original report, certain branched chain compounds or even those containing cyclic structures will form urea complexes provided that there is a sufficiently long straight chain in the molecule and the branch or cycle is not too large. The scope and structural limitations of complex formation have been published (*41, 59, 64, 79, 80, 86*). Thus, benzene and cyclohexane do not form urea complexes, but 1-phenyloctadecane and 1-cyclohexyleicosane, in which the ring is at the end of a long

chain, do. Phenyl hexanoate does not form a urea complex because the straight chain part of the molecule is too short, whereas phenyl dodecanoate does. Methyl 2-methyloctanoate and 2-methylbutyric acid do not form urea complexes whereas the closely related but longer chain compounds, methyl 12-methyltetradecanoate and 3-methylbutyl octanoate, do. 2,2,4-Trimethylpentane and other similarly branched compounds do not form urea complexes under any of the presently known experimental conditions.

In an x-ray study on single crystals (72), urea in the complex is hexagonal, whereas urea itself is tetragonal. In forming the complex, the urea molecules build up in the unit cell in a helical way so that if one could look down the unit cell, one would see a distorted doughnut in which the straight chain organic molecules are able to rest, attached to the ureas by van der Waals' forces, London dispersion forces, or induced electrostatic attractions.

The urea channel is about 6 A. at its widest part and about 5.0 A. at its narrowest. Straight chain hydrocarbons have a cross section of about 4.1 A. and form complexes readily. Hydrocarbons with a single methyl branch require a channel diameter of about 5.5 A. When the straight chain portion of such compounds is relatively short, as in 3-methylheptane, the compound itself does not form a urea complex but forms one readily when it is mixed with a straight chain compound which appears to drag it into the complex (64). When the straight chain part of a singly branched compound is long no difficulty is experienced in obtaining the complex. Compounds with a double branch on one carbon atom, such as 2,2,4-trimethylpentane, require a channel diameter of about 6 A. in all directions and no urea complex has yet been obtained with such materials. Benzene requires a channel diameter of about 5.9 A. and does not form a complex. When the phenyl group is at the end of a long straight chain, a complex forms readily. A reasonable explanation for this is that the phenyl group at the end of a chain is restricted from moving with complete freedom and will therefore be in preferred positions for the formation of complex more often than in the case of benzene itself.

X-ray diffraction patterns of most urea complexes are the same, but they are different from that of urea. Although the x-ray pattern cannot be used to distinguish between or identify specific complexes, if it is doubtful that a complex has been obtained, determination of the x-ray pattern is a simple and rapid confirmatory tool.

Preparation

Urea complexes can be prepared in various ways all of which arrange to bring urea and the compound (or compounds) to be complexed in contact by one means or another. The preparative technique selected depends in part on the solubility and vapor pressure of the compound(s) being studied, whether a high yield or high purity of complex is desired, and, if mixtures are being studied, what degree of separation is wanted. The more important separation techniques are listed and briefly discussed. Many of these techniques are also applicable to the formation of thiourea complexes of branched chain or cycloaliphatic compounds.

1. Bengen's original technique (8, 37, 64) is probably the simplest and most convenient for preparing complexes of pure compounds on a laboratory scale particularly when purity of complex rather than yield is the main consideration. One gram of organic compound is dissolved in 20 ml. of absolute methanol containing 3 grams of urea; if necessary heat is used. If the compound does not dissolve completely, 2-propanol is added dropwise to the hot solution until homogeneity is obtained. The solution is allowed to stand at room temperature for several hours and the long, needlelike crystals are filtered by suction and dried. The filtrate may be cooled to 0° to 10° C. for an additional yield of complex. A blank experiment in which 1 gram of organic compound is dissolved in 20 ml. of methanol or methanol-

2-propanol (urea absent) should also be run. Absence of precipitation in the blank but precipitation in the other is usually positive evidence for complex formation.

2. If it is known from fundamental considerations (8, 52, 64, 86) or from the previous procedure that urea complex formation will occur, a modification of technique 1 is recommended, because high and often quantitative yields of complex (80 to 100%) are obtained. In the modified technique the ratio of organic compound to urea to methanol is 1:4 to 6:7 to 20. For most substances, high yields of pure complex are obtained when the ratio is 1:5:20, and quantitative yields are often obtained when it is 1:5:7, although in the latter case some urea contamination of complex may also occur.

Since urea complex formation is an equilibrium reaction, the larger excess of urea drives complex formation to completion or nearly so (52). In mixtures of complex formers and compounds which do not form complexes, this preparative technique can be used to isolate the complex-formers in the precipitate or the other components in the filtrate after quantitative precipitation of the complexes (15).

3. This technique is a convenient one for the separation of mixtures in which the product sought does not form a urea complex. It also has some merit for the formation of complexes but the time required for completion of complex formation may be inordinately large, especially in large scale operations.

Five grams of mixture, 15 to 35 grams of finely ground urea, 50 to 100 ml. of benzene, Decalin, chloroform or other noncomplex forming solvent, and 1 to 5 ml. of methanol are stirred at room temperature until complex formation is complete. Urea is almost insoluble in the solvent systems used in this technique but is sufficiently soluble and active because of the methanol to permit complex to form and precipitate, thereby setting up a cycle. Noncomplex-formers are isolated from the filtrate (79).

By the use of insufficient urea to form complexes with all the complex-forming components of a mixture, this technique can also be used in fractionation of complex-forming substances by taking advantage of the greater rate of complex formation or the lower solubility of complexes from some of the components.

4. This technique, often called the slurry technique, has been reported to be the basis of a pilot plant separation of certain petroleum hydrocarbons, and it also has considerable merit for use in large scale laboratory preparations (75, 86). In this technique just enough activator and solvent, such as methanol, is added to 25 to 35 grams of urea to wet it and yield a stirrable slurry. Five grams of organic compound is added and stirring is continued until the exothermic reaction is over at which point the mixture is filtered and washed with a noncomplex forming solvent, such as isopentane or iso-octane. The time, which may vary from about 1 to 8 hours, depends on the size of the experiment and the efficiency of heat transfer.

This technique is not generally suitable for preparing pure complexes because of urea contamination. It is a convenient one for separating complex-forming from noncomplex-forming substances, and also for fractionating mixtures of complex-formers by using smaller quantities of urea, as described in the previous technique.

5. In this technique a concentrated aqueous solution of urea and a solution of the organic compound(s), usually petroleum hydrocarbons, in methyl isobutyl ketone are employed. This technique has received detailed study (6, 47). Although its use in fractionating fatty acids has also been reported (47), the partial hydrolysis of urea to ammonium carbonate leads to stubborn emulsions because of the formation of ammonium salts of fatty acids. Ammonium salt formation can be largely eliminated by proper pH control or by minimizing urea hydrolysis. The author has personal knowledge that emulsion formation has been a serious deterrent to the use of this method in the fatty acid industry.

The use of aqueous urea and organic compounds without added solvents has also been reported (8). This method is satisfactory for preparing complexes of pure compounds, but with mixtures technical difficulties arise (25). For example, the complexes are oleophilic and may remain dispersed in the noncomplex-forming oil phase. By the use of surface active agents and electrolytes the complex separates from the oil phase.

6. This techniuqe, also called the desiccator technique, is the most convenient one for preparing complexes of volatile compounds, such as C_6 to C_{10} hydrocarbons (64). Two dishes are placed side by side in a desiccator, one dish containing a known quantity of finely powdered urea, the other an excess of the volatile compound. At suitable intervals, perhaps several hours apart, the desiccator is opened, and the dish containing the urea is rapidly weighed. The operation is repeated until the urea disbt reaches constant weight, at which point complex formation is considered complete. From the original and final weight of

the dish the composition of the complex can be readily calculated. With the more volatile compounds, the desiccator is usually kept in a refrigerator.

7. In this technique, the organic compound(s) and urea are ground in a ball mill (47), or finely powdered urea (2500 to 10,000 mesh) and the compound(s) are mixed (64). Since organic solvents or diluents are usually required to transfer the mixtures and to aid in filtering, this method in effect is similar to some of the preceding ones. It has numerous drawbacks, however, and is apparently rarely used.

Variations on these basic techniques have been described mainly in patents (3, 21, 25, 26, 30, 45, 46, 71).

Table II shows results obtained in the preparation of urea complexes of methyl esters of straight chain fatty acids containing 8 to 18 carbon atoms (37). With the exception of the complex from methyl octadecanoate (stearate) complexes were prepared by technique 1. Yields ranged from 51 to 73%. The complex from methyl octadecanoate was prepared by technique 2; its yield was quantitative. Yields of all of the complexes can be brought above 85% by the use of technique 2.

Table II. Urea Complexes of Methyl Esters of C_8 to C_{18} Fatty Acids

Methyl Ester	Yield, %	Complex[a] Urea to Ester	
		Molar	Weight
Octanoate	59	8.7	3.3
Decanoate	69	9.6	3.1
Dodecanoate	73	11.0	3.1
Tetradecanoate	72	12.2	3.0
Hexadecanoate	66	13.4	3.0
Octadecanoate	100[b]	14.5	2.9
cis-9-Octadecenoate	51	14.4	2.9
trans-9-Octadecenoate	60	13.9	2.8

[a] Prepared by technique 1.
[b] Prepared by technique 2.

The molar ratio of urea to ester is not a whole number and increases linearly with increase in chain length of the ester, but the weight ratio of urea to ester is reasonably constant at 3:1. The somewhat higher ratio observed with the complex of methyl octanoate is undoubtedly a consequence of the relatively high volatility of the ester, which causes some of it to evaporate during the drying and weighing of the complex prior to analysis. Based on approximately 50 complexes prepared in our laboratory, and from a study of the literature, this 3:1 weight ratio appears to be an invariant characteristic of urea complexes of the inclusion type.

Similar quantitative data have been obtained on fatty acids (37), hydrocarbons (64, 86), halides, mercaptans, ketones, and other classes of organic compounds (52, 64).

Analysis

The composition of urea and thiourea complexes can be determined by a variety of chemical and physical methods. Among the chemical methods, functional group analysis is usually the best. Determination of acid or saponification number of a complex permits calculation of the composition of acid or ester complexes, respectively. Urea has a slight saponification number for which a correction must be made. Complexes of unsaturated compounds can also be analyzed directly by the usual halogen absorption methods. Ultimate analysis (carbon, hydrogen, nitrogen, sulfur, halogen) is employed when functional group methods are inapplicable. When both methods are used, the results usually check well. If desired, the complex can be decomposed by addition of hot water to dissolve the urea or by addition of a hot organic solvent in which urea is insoluble to dissolve the included compound(s). Urea or the included compound(s) can be determined by chemical or optical methods (refractive index, optical rotation, ultraviolet and infrared absorption) or by evaporation and weighing the residue.

Of the purely physical methods, the simplest is to note the weight decrease when the complex is exposed to a high vacuum. The weight increase method described under preparative technique 6 is also useful. Both of these methods, however, are appli-

cable to volatile compounds only. Refractometric and calorimetric methods have also been reported (86).

Decomposition

Various methods have been reported for the decomposition of urea and thiourea complexes and reisolation of the included compound(s) (64, 86). The most satisfactory method is addition of water to dissolve the urea, leaving the included compound(s) as an oil or a solid for easy separation. Conversely, the urea complex can be heated with a noncomplexing solvent, such as benzene, iso-octane, or carbon tetrachloride (42) in which urea is insoluble. The included compound(s) will be extracted from the complex. With volatile compounds, quantitative recovery can often be obtained by atmospheric, vacuum, or steam distillation. By distilling through a fractionating column simultaneous decomposition and fractionation of mixed complexes can be effected.

Applications in Petroleum Field

It was only natural that this new technique would be applied to petroleum and its derivatives since many desired separations are difficult to carry out because of small difference in boiling point, the formation of azeotropes, and the low relative reactivity of many of the components.

Separation of straight chain hydrocarbons from crude petroleum fractions is readily accomplished by the use of urea (7, 28, 86). Mixed n-paraffins from about C_7 to C_{50}, depending on the starting stock, can be obtained uncontaminated with branched and cyclic compounds. Fractional distillation of the mixed n-paraffins yields substantially pure individual compounds (7, 16, 56). The noncomplex (filtrate) fraction usually has an extremely low pour point. Reductions in pour point of over 100° F. (5, 7, 23, 28) have been accomplished.

This technique has been used in the preparation of dewaxed lubricating oils without use of refrigeration, low pour point kerosine stocks for use as low vapor pressure jet fuel or for blending with gasoline to be used as high vapor pressure jet fuel, and low pour point distillate fuels from light and heavy stove oils. These separations are more efficient than distillation in lowering the pour point. Increase in the octane number of gasoline by 11 to 12 units has also been accomplished by removal of straight chain components as urea complexes. The mixed straight chain hydrocarbons separated in these processes can be used in wax formulations and to raise the cetane number of Diesel fuel.

Another interesting application is the analysis of petroleum hydrocarbon mixtures for straight chains (31, 87). n-Paraffins containing 14 or more carbon atoms can be precipitated from mixtures substantially quantitatively. For qualitative identification only, the urea complex precipitation procedure can be used with n-paraffins containing as few as 7 carbon atoms. Other literature references are (10, 32, 39, 48, 84). No attempt has been made to review the patent literature completely.

Applications in Fat Field

Separations. The most obvious application is the separation of free fatty acids, which readily form urea complexes, from fats, tall oil, polymerized fatty acids, and other noncomplex-forming substances (14, 44, 47, 54).

Also, urea can be used to fractionate mixtures of fatty acids, esters, alcohols, and other derivatives. There are three main types of separation, namely, separations based on differences in chain length, degree of unsaturation, and branching. In separations based on differences in chain length (34, 41, 61, 70) advantage is taken of the fact that the longer chain compounds form urea complexes preferentially. Therefore, if insufficient urea is employed to combine with all the components of a mixture

Table III. Dissociation Temperatures of Urea Complexes

Acids	Dissociation Temp., ° C.	Methyl Esters	Dissociation Temp., ° C.	Alcohols	Dissociation Temp., ° C.	Miscellaneous	Dissociation Temp., ° C.
Caproic (C_6)	64						
Caprylic (C_8)	73	Caprylate	55				
Pelargonic (C_9)	80.5			Nonanol	57	Vinyl pelargonate	52
Capric (C_{10})	85	Caprate	67	Decanol	68		
Lauric (C_{12})	92.5	Laurate	77.5	Dodecanol	80	Vinyl laurate	79
Tridecylic (C_{13})	96						
Myristic (C_{14})	103	Myristate	96	Tetradecanol	91		
Palmitic (C_{16})	114	Palmitate	118	Hexadecanol	107	Vinyl palmitate	113
Stearic (C_{18})	126	Stearate	132	Octadecanol	124	Vinyl octadecyl ether	125.5
Oleic (C_{18}, cis)	110	Oleate (cis)	110	Oleyl (cis)	98		
Elaidic (C_{18}, trans)	116	Elaidate (trans)	125	Elaidyl (trans)	118		
10-Hendecenoic (C_{11})	90						
9,10-Epoxystearic (cis), m.p. 59° C.	118						
9,10-Epoxystearic (trans), m.p. 55° C.	125						
9,10-Dihydroxystearic, m.p. 95° C.	107	9,10-Dihydroxystearate, m.p. 70° C.	120				
12-Hydroxystearic, m.p. 81° C.	125	9,10-Dihydroxystearate, m.p. 103° C.	114				
12-Ketostearic, m.p. 82° C.	115						

the longer chain components will combine with the urea and precipitate as complexes. For best results, the components to be separated should differ in chain length by at least 4 carbon atoms and preferably by 6. Obviously, when the chain length difference is 6 or more carbon atoms, other separation methods can be used, such as distillation or crystallization; but if the substances are heat labile or if crystallization temperatures required are extremely low—-90° C. for example—the urea method, which is operative at room temperature to 0° C., may be desirable.

The principle in separations based on differences in unsaturation is that as a long chain fatty component becomes more unsaturated it shows greater deviation from the normal straight chain structure. Therefore, at a given chain length, saturated components of a mixture would be expected to form urea complexes preferentially to mono-unsaturated, mono-unsaturated preferentially to di-unsaturated, and so on. Taking advantage of this difference in complex-forming ability, purified saturated (27, 58), oleic (61, 74, 75), linoleic (18, 35, 53, 61, 76), linolenic (35, 76), and more highly unsaturated fatty acids (1, 2, 35), as well as their methyl esters, have been isolated from natural sources. The method has also been applied to alcohols and nitriles (47). No temperature below about 0° C. is required in these separations, whereas the usual fatty acid or ester solvent purification techniques may require crystallization temperatures in the range of −50° to −90° C.

In studies on wool wax and other alcohols (9, 57, 78, 79, 80) as well as other classes of compounds (24, 36, 80, 83), separation of straight chain or only slightly branched compounds from the more highly branched has been accomplished by preferential urea complex formation. In the further fractionation of alcohols, acetylation of the alcohols isolated from the complex, followed by recomplexing, precipitates the acetates of primary alcohols as complexes, leaving the acetates of secondary alcohols uncomplexed and in the filtrate. The purpose of acetylation is to increase the length of the straight chain in the primary alcohols while at the same time enlarging the size of the branched group in the secondary alcohols, thereby permitting a separation of primary from secondary alcohols. On the other hand, certain branched chain compounds, which do not form urea complexes, can be caused to form urea complexes readily by lengthening the straight chain (80). For example, although the methyl- and ethylbutanols and hexanols do not form urea complexes, their esters with long chain fatty acids, such as 3-methylbutyl hexanoate, 2-methylbutyl decanoate, 2-ethylhexyl octanoate, and 2-ethylbutyl decanoate, are complex-forming. The corresponding esters with straight chain acids containing fewer carbon atoms are not complex-forming.
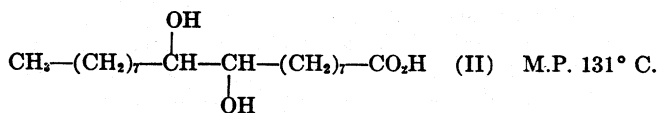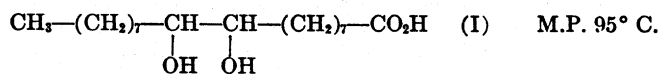
The concept of enlarging the size of a branch to interfere with complex formation or of increasing the length of a chain to enhance it is a relatively new concept and deserves more study.

Storage of Polyunsaturated Fatty Materials. Polyunsaturated fatty materials are readily autoxidized and, generally, cannot be stored satisfactorily for long periods. Urea complexes of unsaturated fatty materials, however, do not autoxidize when exposed to air (61, 62), and this is a convenient way to store labile fatty materials. Reasons for the failure of urea complexes to autoxidize have been given (61). From the structure of the complex it can be seen that the fatty molecules occupy a restricted space in the crystal lattice of the urea. The crystal lattice probably offers a barrier against the free penetration of oxygen, and the restricted space in the lattice is too small to permit the formation of peroxides if oxygen were to penetrate. Furthermore, autoxidation is known to be a chain reaction and it is unlikely that such a mechanism could operate between the strictly separated fatty molecules in the crystal lattice.

Isolation of Fatty Peroxides. Long chain nonterminal peroxides or hydroperoxides are branched in the sense that they contain a bulky group along the straight chain. As was first shown in our laboratory (15), the clean-cut separation of unoxidized (straight chain) from peroxidic material can be accomplished by urea precipitation of the former. The noncomplex (filtrate) fraction consists of the peroxide concentrates (70 to 90% peroxide in the case of methyl oleate peroxides), and yields are usually high. Other workers have investigated this problem (11–13, 33, 44) and have reported only moderate degrees of separation.

Configuration of Diastereoisomers. 9,10-Dihydroxystearic acid contains two asymmetric carbon atoms. Two racemic mixtures are possible and are known. Based on analogy

$$CH_3—(CH_2)_7—\underset{\underset{OH}{|}}{CH}—\underset{\underset{OH}{|}}{CH}—(CH_2)_7—CO_2H \quad (I) \quad M.P. \ 95° \ C.$$

$$CH_3—(CH_2)_7—\overset{\overset{OH}{|}}{CH}—\underset{\underset{OH}{|}}{CH}—(CH_2)_7—CO_2H \quad (II) \quad M.P. \ 131° \ C.$$

with reactions on simple compounds of known configuration, it was concluded (73) that in the low melting isomer (I) the hydroxyl groups are substantially on the same side of the chain whereas in the high melting isomer (II) they are on opposite sides. Reasoning by analogy is often dangerous and an unambiguous way was sought to prove the configuration. Since the size and shape of molecules determine ease of complex formation, the channel diameter required to form a complex from each of the

Table IV. Compounds Forming Thiourea Complexes

Hydrocarbons	Halogen Compounds
2,2-Dimethylbutane	Chloroform
2,3-Dimethylbutane	Bromoform
2,2,3-Trimethylbutane	Iodoform
2,2,4-Trimethylpentane	Carbon tetrachloride
Hexamethylethane	Tetrachloroethane
2,2,3,4-Tetramethylpentane	Hexachloroethane
Decalin	Isopropyl iodide
Cyclopentane	tert-Butyl chloride
Methylcyclopentane	tert-Butyl bromide
Ethylcyclopentane	tert-Butyl iodide
Cyclohexane	Bornyl chloride
Methylcyclohexane	Chlorocyclohexane
Alkylcyclohexanes	
Cyclohexene	Alcohols
3-Ethyltetracosane	
1,1-Dimethylcyclopentane	Cyclohexanol
1,1,2-Trimethylcyclopentane	Pinacol
1-Methyl-1-ethylcyclopentane	Borneol
cis-1-Methyl-3-ethylcyclopentane	Trichlorotrimethylcarbino
trans-1-Methyl-3-ethylcyclopentane	
1-Cyclohexyloctane	Ketones
1-Cyclohexyleicosane	
1,4-Di-n-decylcyclohexane	Methyl isobutyl ketone
exo-perhydro-4,7-methanoindene	Pinacolone
2-Cyclohexyleicosane	Cyclohexanone
1,2-Dicyclohexylethane	Alkylcyclohexanones
1-Cyclohexyl-3-cyclopentylpropane	Cyclopentanone
1-Phenyl-2-cyclohexylethane	Menthone
1-Cyclopentylheneicosane	Pulegone
Dicyclopentyl	Camphor
cis (0,3,3) Dicyclooctane	Cyclohexenone
1,3-Dicyclopentylcyclopentane	Thujone
Menthane	p-Methyl trimethylacetophenone
Pinane	
Camphane	

dihydroxystearic acids was calculated, assuming the reported structures were correct (73). The low melting isomer required about 5.4 A.; the high melting about 6 A. Therefore, the high melting isomer should not form a urea complex whereas the low melting isomer should form one readily. Experimentally the high melting isomer gave a 0% yield of complex and the low melting isomer almost a 100% yield (77). This work has recently been independently confirmed (82).

Dissociation Temperatures of Urea Complexes. All urea inclusion complexes have been reported to have the melting point of urea (64). Therefore, there must be some temperature at which the complex decomposes into its components, which presumably are immiscible, and the urea melting point is observed (37). This initial temperature of decomposition, which has been defined as the dissociation temperature (37), can be readily observed by slowly heating several crystals of transparent complex on a Kofler hot stage attached to a low or medium power microscope. When decomposition ensues the transparent crystals become milky. Repetition on a fresh sample permits duplication of the dissociation temperature of any particular complex to ±1.5° C. Table III lists the dissociation temperatures of urea complexes of approximately 40 fatty compounds. In each homologous series the dissociation temperatures of complexes of adjacent or closely adjacent members are sufficiently far apart to permit identification. This is in contrast to the melting points of the common derivatives of long chain compounds. If the dissociation temperature for each of the four homologous series in Table III are plotted against number of carbon atoms, straight lines are obtained which converge about the melting point of urea. For a given number of carbon atoms the most stable complexes are obtained with the acids, then the alcohols, the methyl esters, and the vinyl esters.

The sensitivity of dissociation temperatures and their use in structure work are best illustrated by comparing the dissociation temperatures of several cis-trans pairs (oleic-elaidic acids, cis and trans-9,10-epoxystearic acids, methyl oleate-elaidate, and oleyl-elaidyl alcohols). In each pair the vapor pressure and number of carbon atoms is the same but the dissociation temperature of the trans isomer is significantly higher than that of the cis isomer. The complex of the trans isomer is more stable, even though the secondary valence forces involved in the formation of

complexes from cis-trans pairs are identical. Examination of molecular models of cis-trans isomers shows that the trans isomers have little or no additional spatial requirements in the urea channel over those of the corresponding saturated compounds (cross section, about 4.1 A.). In contrast, the cis compounds have slightly greater spatial requirements and slight distortion of the normal shape of the long chain molecule must occur for it to be accommodated in the urea channel. Thus, with cis compounds some strain is present thereby yielding a less stable complex, which is reflected in the dissociation temperature.

Separation of Optical Isomers

A novel application of urea complexes has been described by Schlenk (63, 67), and only a limited amount of information is available on it. If a urea complex is prepared from any substance, all the crystals of complex will have either a right hand or left hand helix. This is determined solely by chance. If a urea complex is prepared from a racemic mixture, crystals of complex will be obtained which can be symbolically represented, assuming that a right hand helix forms, as D-form–right hand helix and L-form–right hand helix. These, of course, are no longer mirror images and should have slightly different solubilities. Therefore, if a racemic mixture is treated with insufficient urea to precipitate the compound completely as complex, the isomer which preferentially precipitates will be the one whose complex has the lower solubility, and a slight concentration of it will be accomplished. A few crystals of this complex are reserved; the remaining crystals are decomposed, and the regenerated compounds are again treated with insufficient urea to precipitate all the material. The solution, however, is first seeded with the crystals which have been reserved for this purpose. This ensures that the same direction of helix will form as in the first case and an additional concentration of the same isomer will be achieved. This process, repeated many times, will ultimately separate optical isomers. Separation of the chlorooctanes has been accomplished and it has been mentioned, but no details given, that the absolute configuration of amino acids can be determined.

Thiourea Complexes

Another important class of inclusion complexes are the thiourea complexes. Thiourea complexes with organic compounds were discovered independently by Fetterly (20, 21) and by Angla (4) in the middle nineteen forties. In substantially every respect, thiourea is similar to urea with the exception of the types of compounds with which it forms complexes. Thiourea forms complexes with many branched chain and cycloaliphatic compounds, but generally not with straight chain compounds, aromatics, and terpenes (4, 20, 21, 22, 51, 65). Urea and thiourea separation techniques complement each other. Originally it was thought that thiourea did not form complexes with any straight chain compounds but it was recently reported (43, 66) that n-paraffins with 16 or more carbon atoms will form thiourea complexes at 0° C. or even at as high a temperature as 25° C., n-tetradecane will form a thiourea complex at 0° C. but not at 25° C., and paraffins with 12 or fewer carbon atoms do not form thiourea complexes even at 0° C. Thiourea complexes with n-paraffins have low stability.

Table IV lists some compounds reported to form complexes with thiourea. None of these forms urea complexes. Although aromatic compounds generally do not form thiourea complexes, specific ones will in which a predominating part of the molecule is highly branched—e.g., p-methyl trimethylacetophenone. The molar ratio of thiourea to hydrocarbon is somewhat lower than the molar ratio of urea to straight chain hydrocarbons (51, 65).

X-ray data on thiourea complexes have been published (29, 68, 72). The unit cell of thiourea in the complex is rhombohedral

and the arrangement of the thiourea molecules is similar to that of urea molecules in urea complexes. The larger size of the sulfur atoms, however, results in a larger channel, about 8 A. in diameter, in which branched or cyclic compounds fit.

Methods of preparation, isolation, analysis, and decomposition of thiourea complexes are essentially the same as for urea complexes. The lower stability of thiourea complexes requires that more precautions be taken in their handling and storage.

In conclusion, a new and powerful separation technique is now available which involves the preparation and precipitation of crystalline complexes between urea and straight chain compounds and thiourea and branched or cycloaliphatic compounds. These techniques permit the isolation of many components in a readily handled, stable crystalline form. Since the techniques are primarily dependent on the size and shape of molecules, compounds which formerly have been difficult to separate, or supposedly impossible, can in many cases be separated quantitatively.

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